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Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go?

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Atopic dermatitis (AD) is a paradigmatic chronic inflammatory skin disease characterized by a complex pathophysiology and a wide spectrum of the clinical phenotype. Despite this high degree of heterogeneity, AD is still considered as a single disease and usually treated according to the “one-size-fits-all” approach. Thus more tailored prevention and therapeutic strategies are still lacking. As for other disciplines, such as oncology or rheumatology, we have to approach AD in a more differentiated way (ie, to dissect and stratify the complex clinical phenotype into more homogeneous subgroups based on the endophenotype [panel of biomarkers]) with the aim to refine the management of this condition. Because we are now entering the era of personalized medicine, a systems biology approach merging the numerous clinical phenotypes with robust (ie, relevant and validated) biomarkers will be needed to best exploit their potential significance for the future molecular taxonomy of AD. This approach will not only allow an optimized prevention and treatment with the available drugs but also hopefully help assign newly developed medicinal products to those patients who will have the best benefit/risk ratio. (*J Allergy Clin Immunol* 2017;139:S58-64.)

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder.¹ The disease represents a substantial socioeconomic burden,^{2,3} partly because of the lack of an efficient therapeutic armamentarium able to control the disease in the long term.⁴ Most of the physicians who take care of patients with AD are well aware of the high degree of heterogeneity of the clinical phenotype and the debated role of IgE-mediated sensitization or food allergy.^{5,6} The latter is only one among many provocative factors claimed to be instrumental in inducing flares and/or supporting the chronic inflammation and itching sensation.

Our current understanding of the disease has dramatically evolved over the last years, mainly because of substantial progress in epidemiology and genetics, further supporting the concept of the atopic march⁷ but also unraveling new aspects with regard to the natural history^{8,9} and persistence of AD over a lifetime.^{10,11} Many pioneering discoveries have unraveled the critical genetic predisposition underlying epidermal barrier dysfunction,^{12,13} as well as the intimate immunologic mechanisms working as forces driving chronic inflammation,¹⁴ and triggering the emergence of IgE-mediated sensitization¹⁵ and contact sensitization.¹⁶

Despite the obvious complexity of the clinical phenotype, we are still treating AD according to the “one-size-fits-all” approach and are neglecting a more differentiated method based on stratification of AD.^{17,18} Change will come through a better understanding of the different genetic and immunologic mechanisms underlying the wide spectrum of disease phenotypes. The roadmap toward a precision medicine approach in AD management will be mainly dictated by the discovery and validation of reliable biomarkers that will enable the physician

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Abbreviation used
AD: Atopic dermatitis

including strong lichenification, typically appear later and are sometimes combined into more nodular lesions corresponding to the prurigo phenotype. Except for the very initial stage of the disease during the first weeks of life, pruritus remains a typical hallmark in all stages.

Infantile AD (between 3 months and 2 years of age). The first lesions emerge around the second month of life and typically affect the cheeks with edematous papules and papulovesicles. They can form large plaques with oozing and crusting. The scalp also shows extensive scaling of the so-called cradle cap. Furthermore, the scalp, neck, and extensor parts of the extremities, as well as the trunk, can be involved, sparing the diaper area. Most importantly, the very initial stage of the disease might be very difficult to diagnose, whereas the more typical eczematous lesions on respective localizations can appear a few weeks later.

Childhood AD (age 2-12 years). At this stage, acute lesions still appear, but chronic lesions with some lichenification tend to be at the forefront. The predilection sites are the popliteal and antecubital fossa (flexural eczema), as well as the periorificial areas on the head. Quite often, the hands and wrists show rather nummular plaques with oozing and crusting corresponding to a nummular type of the disease. Dry skin (xerosis) becomes more dominant.

AD in adolescents and adults (age >12 up to 60 years). In this period of life, the lesions are more fixed to classical areas, such as the head, neck, and flexural areas. Moreover, in adults the disease can also affect the hands (chronic hand dermatitis). In female subjects the disease also often involves the periorbital areas. In patients with a long-standing natural history of the disease, AD is more likely to have an extensive and sometimes erythrodermic aspect.

to provide more tailored management, starting from prevention strategies and moving up to treatment of patients with more severe disease with targeted therapies.¹⁹⁻²¹ A clear definition of different clinical phenotypes on the one hand and potential biomarkers providing the adequate respective endophenotypes are key elements for successful development of new therapeutic options²² and implementation of precision medicine in patients with AD.

CLINICAL PHENOTYPES Stratification based on the age-related clinical picture

The clinical picture of AD varies substantially depending on the age of the patient.¹ Typically, at least 4 different kinds of clinical features have been defined²³ as follows: infantile, childhood, adolescent/adult, and elderly. Although acute lesions predominate more in the infantile spectrum, chronic lesions,

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AD in the elderly (age >60 years). This seems to be a rather underestimated clinical phenotype of AD (see “Natural history of AD”). This form is mostly characterized by extensive eczematous lesions up to erythrodermic aspects with a strong pruritic component. Sometimes the lesions spare the flexural areas. This particular phenotype certainly needs a more profound analysis to define clear-cut clinical criteria for its definitive diagnosis. In the elderly a number of differential diagnoses should be excluded that might mimic AD, such as allergic contact dermatitis and cutaneous T-cell lymphoma.

Stratification based on disease severity

As already mentioned, AD can cover a wide spectrum in terms of severity, ranging from very mild to very severe phenotypes. In addition to the classical diagnostic criteria, the definition of severity as mild, moderate, or severe is best obtained by using validated scoring systems, such as the SCORAD or Eczema Area and Severity Index scores. For the purposes of pivotal (phase 3) clinical trials, some regulatory agencies, such as the US Food and Drug Administration, request the so-called Investigator Global Assessment as a primary end point with a 5- or 6-point scale that has never been properly validated. An attempt to align these different scoring systems in a single chart is presented in Fig 1

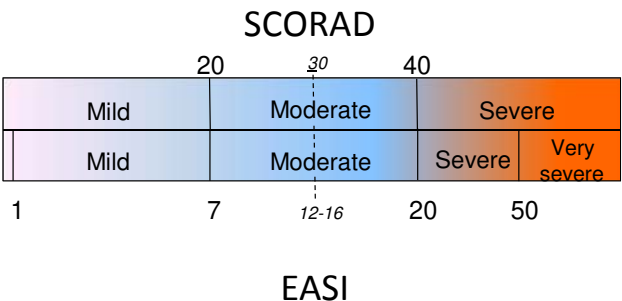


FIG 1. Clinical phenotype: stratification according to severity, as exemplified by SCORAD and Eczema Area and Severity Index (EASI) scores (based on Lessem et al²⁴).

(based on Leshem et al²⁴). Such an alignment might be useful to compare the efficacy of primary or secondary end points from different studies, such as in a meta-analysis. There is still debate as to which scoring system is the easiest to use for physicians in daily practice, who face therapeutic decisions involving new active substances, such as biologics.

The so-called atopic stigmata, which represent clinical findings apart from eczematous lesions, might also represent particular variants of the mild forms of AD and are more helpful for a classification in relationship to the atopic diathesis.²⁵

Stratification based on age of onset

Another way to stratify patients affected by AD is to classify them according to the natural history of the disease. This has many implications for our understanding of epidemiologic aspects and for our understanding of the dynamics of the disease, which can be imprinted by different kinds of immunologic mechanisms. Finally, being able to identify those patients with the highest risk of an ongoing chronic inflammation and a long-term disease history would provide significant progress in the targeted approach to prevention through early intervention. Although in the past AD was traditionally considered a disease primarily occurring in childhood and potentially resolving in a complete and definitive remission in more than 50% of patients up to age 10 years, more recent epidemiologic evidence supports the concept that, once acquired, AD can persist for the rest of a patient's life.

Follow-up studies of patients and retrospective analyses have identified at least 6 different types of onset of AD. In agreement with the notion that such phenotypes might represent distinct subentities is the observation that they are influenced by different environmental exposures effective at different ages. In support of this assumption, prenatal maternal contact with animals goes along with protection against AD manifesting during the first year of life,²⁶ whereas feeding habits during the first year of life are associated with AD with an onset after the first year of life.^{27,28} These types of onset are summarized in Fig 2⁹ and described below.

Very early onset (between 3 months and 2 years).

Depending on epidemiologic studies, this type of onset represents 60% to 80% of all forms of AD onset. A substantial portion of patients can go into complete remission before age 2 years. Another portion, which is estimated roughly at 40%, continues to have the disease over a longer period of time and could represent the population with the highest risk for the atopic march.

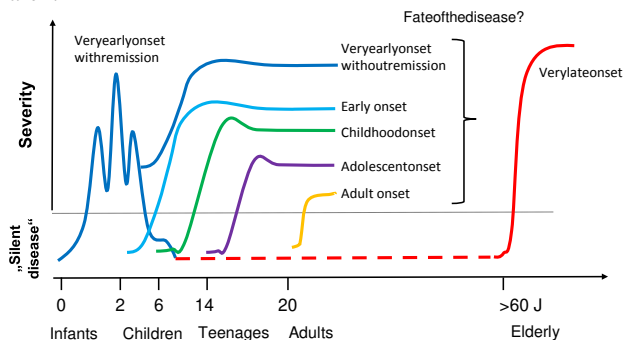


FIG 2. Clinical phenotype: stratification according to age of onset. Curves indicate age of onset and possible natural histories (based on Garmhausen et al⁹).

Early onset (between 2 and 6 years). Early onset represents another subgroup of the phenotype in terms of age of onset, and these patients also bear a high risk of having chronic disease.

Childhood onset (between 6 and 14 years)

Childhood onset represents a rather small group of patients (approximately 10%) for whom the fate of the disease has not clearly been explored.

Adolescent type of onset (between 14 and 18 years)

Adolescent onset represents probably the smallest group (<10%), for which there are only limited epidemiologic data about the fate of the disease.

Adult onset (between 20 and 60 years). Adult onset is an interesting group, representing about 20% of the overall population, and is characterized mainly by female patients with a rather mild clinical phenotype and a very limited spectrum of sensitization, usually accompanied by a normal total IgE level.

Very late onset (>60 years). The group with very late onset has been identified more recently²⁹ and seems to represent a subgroup of increasing significance. Within this group of old patients, at least 2 further subgroups can be identified: those who had AD in the past but had a longer period of remission and those who start the disease very late in life.³⁰ Very often, these patients present with a rather severe form of the disease and high total IgE levels. Clearly, as is the case for the very early onset group between 3 and 6 months, clear criteria for the diagnosis of this particular group in the older generation are missing.

Stratification based on ethnic origin of the patients

For a long time, it has been assumed that the clinical picture of AD is identical, irrespective of the world region and ethnic origin of the patients. Recently, a pioneering work addressing the transcriptomic profile of white patients and patients from Asian populations suggested that there might be substantial differences in the profile of the cytokines driving chronic inflammation in the latter populations.³¹ In addition to the expected T_H2 profile, patients from Japan and Korea also have strong T_H17 expression in skin lesions. This observation correlates with histologic changes showing more pronounced epidermal hyperplasia and, clinically, an overall more pronounced lichenification of the lesions. On the other hand, the clinical picture of AD lesions in African Americans has also been reported to be different from the classical picture described in the white population.³² Also, pathophysiologic differences have been observed because, for example, filaggrin deficiency, which is commonly found in white patients, was not observed in South African patients with AD.³³ Therefore it is likely that further studies will show variations of the clinical phenotype depending on the ethnic origin of the patients and that this phenomenon is mirroring significant differences in the pathomechanisms underlying chronic inflammation. This is further supported by the observation of different hotspots in the filaggrin mutations reported between white and Asian populations.³⁴ It cannot be

excluded that some of the diagnostic criteria mainly generated and validated in the white population will have to be revised and adapted according to other ethnic variants of AD. Further evidence for the need of a more adapted diagnostic approach has been provided in a recent analysis in Chinese children.^{35,36} Ultimately, this might have a profound effect on therapeutic strategies involving new active substances targeting cytokines and other structures assumed to be key players in the respective subgroup of patients worldwide.

ENDOPHENOTYPES AND BIOMARKERS:

MANDATORY TOOLS FOR STRATIFICATION OF AD

According to the World Health Organization, biomarkers are considered as “any substance, structure or process that can be measured in the body or its products and influences or predicts the incidence of outcome of disease or disease.” Moreover, according to the definition of the National Institutes of Health Biomarker Definition Working Group,³⁷ “a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention.” Hence any kind of measurable characteristic that bears a diagnostic, prognostic, or predictive value can be considered a biomarker.

Endophenotypes are defined as measurable components unseen by the unaided eye along the pathway between disease and distal genotype.³⁸ Thus the endophenotype is made of a collection of biomarkers between the clinical phenotype and genotype. Ultimately, this individual biosignature might also include data obtained from their environmental life (ie, the exposome). In fact, in addition to the clinical phenotype, biomarkers and endophenotypes are now considered fundamental tools that will enable us to stratify highly complex diseases into subgroups for which more tailored prevention and therapeutic strategies have to be developed. More than individual biomarkers, it is expected that a combination or a panel of different biomarkers will be used for the stratification of complex phenotypes, as we already learned from the field of oncology, in which therapeutic decisions are taken more and more often based on this kind of approach.

In contrast to the clinical phenotypes, the biomarker discovery and definition of endophenotypes is only at an early stage and represents a substantial unmet need. Hence there is no clear endophenotype defined for AD. In the context of precision medicine, at least 7 different types of biomarkers can be considered for AD (Table I).³⁹ It should be emphasized that none of the mentioned candidate biomarkers have reached the step of validation thus far.

TABLE I. Subtypes of candidate biomarkers in AD

Biomarker	Screening	Diagnostic	Severity	Sensitization	Predictive therapeutic response	Prognostic fate of AD/comorbidities
Total/specific IgE				111	Potential for prevention	?
TARC/CCL17	1					
MDC/CCL22			1			
CTACK/CCL27			111			
FLG1/2	11		1		Potential for prevention	?
SPINK5/LEKTI	1					?
TSLP	1	1				Risk for viral complication
IL-31						
IL-33				?		Risk for viral complication
IL-22						
FcεRI/FcγRII						
IDO			1			Risk for EH
LL-37			1			
IL-18			1			
IL-16						
Soluble IL-2 receptor						
PARC/CCL18			1			
TEWL	11		1	?	Potential for prevention	?
Periostin			1			
BDNF			1			
IgE against <i>Malassezia</i> species			1			1

BDNF, Brain-derived neurotrophic factor; CTACK, cutaneous T-cell-attracting chemokine; EH, eczema herpeticum; FLG, filaggrin; IDO, indolamine-2,3-dioxygenase; MDC, macrophage-derived chemokine; PARC, pulmonary and activation-regulated chemokine; SPINK5/LEKTI, serine protease inhibitor Kazal-type 5/lympho-epithelial Kazal-type-related inhibitor; TARC, thymus and activation-regulated chemokine; TEWL, transepidermal water loss; TSLP, Thymic stromal lymphopoietin.

Screening biomarkers allowing identification of patients with high risk of AD before first clinical signs of the disease

With regard to the natural history of AD in infancy and childhood, it would make sense to use screening biomarkers to identify those newborns at high risk of AD. Because it has been shown that early intervention directly after birth in such a subpopulation selected on the basis of family history might at least delay the appearance of the disease,^{40,41} the question arises of which biomarker or biomarker combination would allow us to select those newborns who will potentially have the best benefit from this kind of early intervention. Recently, it has been reported that measurement of transepidermal water loss could be a simple and noninvasive method to select these subjects.⁴²

Screening for mutations and variants in the genes encoding epidermal structural proteins, such as filaggrin 1 and 2,⁴³ would also represent a potential way to identify subjects with a high risk of having AD⁴⁴ and undergoing the atopic march.⁴⁵ Although genotyping still remains a rather cumbersome and

expensive approach, it is expected that this technology will be applicable for screening approaches in the near future. Similarly, exploring the risk for AD based on analysis of mutations and variants of other genes encoding for structural proteins, such as serine protease inhibitor Kazal-type 5/lympho-epithelial Kazal-type-related inhibitor (SPINK5/LEKTI)⁴⁶ or thymic stromal lymphopoietin,⁴⁷ could be useful to detect populations at high risk of disease.

Diagnostic biomarkers helping in early diagnosis of the disease and in the case of differential diagnostic problems

Although the diagnosis of AD is performed mainly based on clinical signs, physicians are struggling at the 2 ends of the age spectrum: the very early phase of life before the age of 3 to 4 months and in the elderly, as mentioned above. Unfortunately, none of the currently available biomarker candidates^{48,49} have been tested in these 2 particular situations, and therefore there is clearly an unmet need in the field of biomarker discovery to answer this crucial question.

Severity biomarkers that can be used as support in clinical trials for evaluation of therapeutic success and/or as surrogate markers for therapeutic response in the context of long-term disease control

Most of the potential biomarkers described thus far in the literature are more or less related to the issue of severity and their changes during the therapeutic regimen. Among these, thymus and activation-regulated chemokine (CCL17), macrophage-derived chemokine (CCL22), cutaneous T-cell-attracting chemokine (CCL27), IL-31, IL-33, IL-22, LL37, IL-18, IL-16, pulmonary and activation-regulated chemokine (CCL18), periostin, and the soluble IL-2 receptor and brain-derived neurotrophic factor are the most prominent candidates.⁵⁰⁻⁵⁹ Also, sensitization to skin-colonizing yeast, such as *Malassezia* species or autoallergens, has been described as a possible marker of disease activity⁶⁰ and also for autoimmunity (see below). However, because the clinical effect of a therapeutic strategy is best appreciated based on objective evaluation by the physician and patient, the value of this kind of biomarker in the context of clinical trials and in real-world dermatologic practice remains rather limited.

Biomarkers assessing the individual sensitization profile

Obviously, measuring total IgE levels and, more particularly, specific IgE levels is a useful way to appreciate the sensitization profile of a given patient not only as a screenshot but also in follow-up during the natural course of the disease. The dichotomic view of AD⁶¹ in intrinsic (also called atopiform) versus extrinsic forms remains questionable^{62,63} because it is mainly based on measurement of total IgE levels and a limited panel of specific IgE levels in a given subject.⁶⁴ Thus, rather than 2 completely different forms of AD, the so-called intrinsic and extrinsic forms of AD most probably represent 2 opposite parts of one spectrum of the disease. Indeed, variations in dominance in the cytokine profile might account for this phenomenon. Clinical practice has shown that there is a significant proportion of patients with seemingly normal total IgE levels (ie, <100 kU/mL) but who also have significant specific IgE levels against common allergens, such as pollen, house dust mite, or some particular food allergens. Therefore, more than the total IgE level, determination of the ratio of a given specific IgE level to the total IgE level might be a more useful biomarker to evaluate more objectively the sensitization profile and the potential usefulness of particular therapeutic interventions, such as allergen-specific immunotherapy. With increasing insight into sensitization on a molecular level, this might also contribute to the discovery of more subentities of AD.⁶⁵ Moreover, it has been shown that there is a phenomenon of sensitization against self-proteins in both children and adults,⁶⁶ suggesting that at least some of the patients can display a particular form of AD, which can be considered an autoimmune form of the disease.^{67,68} Therefore a refinement and standardization of the technology to measure specific IgE levels directed against autoallergens represents another interesting unmet need to address. Indeed, the presence of such specific IgE against self-protein would imply that avoidance of classical environmental allergens, including pollen, house dust mite, or food, might be useless in this subpopulation of patients.

Predictive biomarkers for the therapeutic response and/or risk of side effects for a given active substance (pharmacogenomics)

In contrast to the forthcoming biologics targeting particular cytokines instrumental in the pathomechanisms of the disease,^{69,70} the thus far available therapeutic strategies are rather unspecific. Therefore the biomarker discovery in the field of therapeutic response remains completely neglected thus far. However, with regard to the knowledge accumulated recently in our understanding of the possibly diverging mechanisms driving chronic inflammation in children versus adults on the one hand and potentially also in different ethnic populations, the quest for biomarkers predicting the therapeutic response will be of significant importance. For example, the fact that AD in childhood shows a T_H2, T_H9, and T_H17 polarization and in adults the T-cell response seems more T_H22 dominant^{71,72} would suggest that current biologics targeting T_H2 cytokines would be even more effective in children than in adults. Similarly, a potential T_H17 dominance in the Asian population would allow the option to use anti-IL-17 biologics typically approved for psoriasis.

Some biomarkers providing reliable information on the compliance of the patient would be helpful. Such biomarker-based endophenotypes will have the potential to guide future therapeutic decisions based, for example, on analysis of the transcriptomic profile in the blood and skin. This new strategy has great potential in pharmacoeconomics in the era of personalized medicine when it comes to use of expensive targeted therapy options.

Prognostic biomarkers that might predict risk for the atopic march, long-lasting remission phases, or comorbidities

This type of biomarker is of utmost importance in the management of AD. Indeed, we learned from epidemiologic studies that the natural history of the disease (see above) and the thereby associated comorbidities, complications, or both are probably confined to some particular subgroups of patients. Prognostic biomarkers able to provide key information on the fate of the disease in childhood (ie, occurrence of remission before adolescence or continuous ongoing chronic inflammation) and, most importantly, the emergence of allergic asthma represent another unmet need that deserves to be addressed. Also, the risk of severe viral complications,⁷³ such as eczema herpeticum, could be predicted.⁷⁴ Moreover, because we learned that AD might represent a lifelong disease^{10,11} with potential phases of low activity levels and later reactivation, the availability of such prognostic biomarkers predicting this stage of life would be very helpful in terms of prevention of AD in older patients and the possible associated comorbidities.⁷⁵

UNMET NEEDS FOR STRATIFICATION OF AD IN THE ERA OF PRECISION MEDICINE

A number of issues must be addressed to be able to provide a meaningful and practical stratification strategy for the clinical phenotype linked to more tailored preventative and therapeutic

approaches. This will help us reach the ultimate goal of precision medicine for AD and facilitate drug development. There is an increased number of biomarker candidates that have recently been identified in the context of our pathophysiologic understanding of this disease. However, as shown in Table I, there are a number of fields in biomarker discovery that urgently need to be addressed to be able to enrich the panel of biomarkers with these different aims. By essence, biomarker discovery is a dynamic field very much related to emerging concepts in pathophysiology, as well as progress in the extended field of “omics.” Ideally, detailed and high-quality phenotypical information from patients of large cohorts, as well as control subjects collected in registries and flanked biobanks, are key for biomarker discovery and validation and should be the focus of future research programs. This is the strategy followed by the

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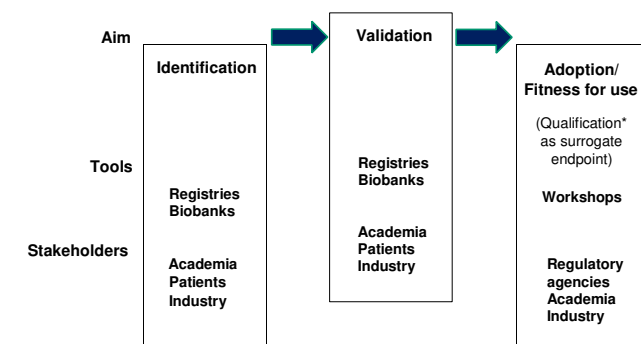


FIG 3. From biomarker discovery to fitness for use: steps of biomarker development until use in clinical trials or practice. None of the mentioned candidate biomarkers (Table I) have reached the step of validation.

CONCLUSION

AD is not a life-threatening disease but has a dramatic effect on quality of life of patients and their relatives and thereby represents a significant socioeconomic burden. It is still considered a single disease, and in addition to severity, disease management currently does not consider its highly heterogeneous clinical phenotype. It usually neglects the high rates of nonresponsiveness to this classical approach and the opportunities for prevention measures. This is especially valid for a substantial proportion of patients with AD of early onset, which is considered the first step in the development of other atopic disorders, such as allergic rhinitis, asthma, and food allergy (ie, the starting point of the atopic march).

Thus, as in the field of oncology, where the discovery of biomarkers as companion diagnostics is becoming a key element in the development of new prevention and therapeutic strategies, the identification of new biomarkers in the field of dermatology and allergy bears a high potential for many purposes, such as diagnostic or prognostic algorithms. As we are now entering the era of stratified medicine, such biomarkers will play a fundamental role in improving management, with the potential to interfere in the ongoing pathophysiologic process through implementation of disease-modifying strategies.

Christine K€uhne—Center for Allergy Research and Education consortium (<https://www.ck-care.ch/en/ck-care>).

Systems biology approaches will help to merge the information from clinical phenotypes with the increasing amount of data generated by using candidate biomarkers in this context to define reliable endophenotypes. Moreover, in addition to the validation issue, the fitness for use and qualification of biomarkers (Fig 3), particularly for those with a potential to be used as surrogate end points in clinical trials, will have to be addressed to implement use of these biomarker in daily practice. Merging the clinical phenotypic data from the registries from patients with AD with the newly discovered biomarkers from the biobank will potentially lead to a new molecular taxonomy of the disease, representing the groundwork for precision medicine.

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